

10/551152

JC20 Rec'd PCT/PTO 28 SEP 2009

EXHIBIT A

**International Search Report corresponding to
PCT Application No. PCT/US2004/009380**

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US2004/009380

| A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D225/02 C07D313/00 C07D405/06 C07D495/04 A61K31/365 A61K31/435 A61P35/00 C07C13/02 //(C07D495/04, 333:00, 235:00) | | | | | | | | | | | | | | |
|--|--|--|---|--|-----------------------|---|--|---------------------------|---|---|---------------------------|-----|--|--|
| According to International Patent Classification (IPC) or to both national classification and IPC | | | | | | | | | | | | | | |
| B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D A61K C07C | | | | | | | | | | | | | | |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched | | | | | | | | | | | | | | |
| Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, CHEM ABS Data | | | | | | | | | | | | | | |
| C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category *</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X</td> <td>GAUL C ET AL: "Synthesis of the macrolide core of migrastatin" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 43, no. 50, 9 December 2002 (2002-12-09), pages 9039-9042, XP004391896 ISSN: 0040-4039 Cpds. 1, 13, Schemes 1,2</td> <td>14-26, 30-41, 43-47</td> </tr> <tr> <td>X</td> <td>NAKAMURA ET AL.: "Absolute Configuration of Migrastatin, a Novel 14-Membered Ring Macrolide" THE JOURNAL OF ANTIBIOTICS, vol. 55, no. 4, April 2002 (2002-04), pages 442-444, XP009035010 ISSN: 0040-4039 Cpd. 2</td> <td>14-26, 30-41, 43-47</td> </tr> <tr> <td colspan="3" style="text-align: center;">-/-</td> </tr> </tbody> </table> | | | Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. | X | GAUL C ET AL: "Synthesis of the macrolide core of migrastatin" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 43, no. 50, 9 December 2002 (2002-12-09), pages 9039-9042, XP004391896 ISSN: 0040-4039 Cpds. 1, 13, Schemes 1,2 | 14-26, 30-41, 43-47 | X | NAKAMURA ET AL.: "Absolute Configuration of Migrastatin, a Novel 14-Membered Ring Macrolide" THE JOURNAL OF ANTIBIOTICS, vol. 55, no. 4, April 2002 (2002-04), pages 442-444, XP009035010 ISSN: 0040-4039 Cpd. 2 | 14-26, 30-41, 43-47 | -/- | | |
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| -/- | | | | | | | | | | | | | | |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. | | | | | | | | | | | | | | |
| * Special categories of cited documents : <table border="0"> <tr> <td style="vertical-align: top;"> "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed </td> <td style="vertical-align: top;"> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "A" document member of the same patent family </td> </tr> </table> | | | "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed | "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "A" document member of the same patent family | | | | | | | | | | |
| "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed | "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "A" document member of the same patent family | | | | | | | | | | | | | |
| Date of the actual completion of the international search 14 September 2004 | | Date of mailing of the international search report 21/09/2004 | | | | | | | | | | | | |
| Name and mailing address of the ISA Europaan Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016 | | Authorized officer Fritz, M | | | | | | | | | | | | |

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2004/009380

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|--|---------------------------|
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | <p>WOO ET AL.: "Migrastatin and a New Compound, Isomigrastatin, from <i>Streptomyces platensis</i>" THE JOURNAL OF ANTIBIOTICS, vol. 55, no. 2, February 2002 (2002-02), pages 141-146, XP009035019 ISSN: 0040-4039 Compound "isomigrastatin" page 142</p> <p>-----</p> | 14-26, 30-41, 43-47 |
| X | <p>US 2002/119937 A1 (CARNEY JOHN ET AL) 29 August 2002 (2002-08-29)</p> <p>abstract</p> <p>-----</p> | 14-26, 30-41, 43-47 |
| X | <p>TAKEMOTO ET AL.: "Migrastatin, a Novel 14-Membered Ring Macrolide, Inhibits Anchorage-independent Growth of Human Small Cell Lung Carcinoma Ms-1 Cells" THE JOURNAL OF ANTIBIOTICS, vol. 54, no. 12, December 2001 (2001-12), pages 1104-1107, XP009035020 ISSN: 0040-4039 the whole document</p> <p>-----</p> | 14-26, 28-41, 43-47 |
| X | <p>"MIGRASTATIN, A NOVEL 14-MEMBERED LACTONE FROM STREPTOMYCES SP, MK929-43F1" JOURNAL OF ANTIBIOTICS, JAPAN ANTIBIOTICS RESEARCH ASSOCIATION. TOKYO, JP, vol. 53, no. 10, October 2000 (2000-10), pages 1228-1230, XP002938945 ISSN: 0021-8820 the whole document</p> <p>-----</p> | 14-26, 30-41, 43-47 |

INTERNATIONAL SEARCH REPORT

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PCT/US2004/009380

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-13, 27
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 1-13,27

Present claims 1-13 relate to an extremely large number of possible compounds, as the term "composition" alone also designates the compound itself.

Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Furthermore the initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

Also for these reasons, a meaningful search over the whole breadth of the claim is neither possible nor reasonable

Consequently, the search has been restricted to the compounds according to the structural formulas displayed in claim 14 in which

R1, R2 designate hydrogen
R3, R5 and R6 designate a methyl group

The subsequent claims were considered dependent from claim 14

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/009380

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| US 2002119937 | A1 | 29-08-2002 | NONE |